Flomax®

(tamsulosin hydrochloride)

Capsules

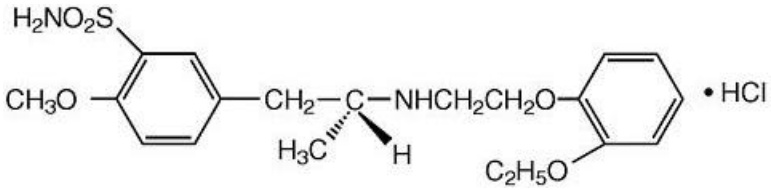
Prescribing Information

DESCRIPTION

Tamsulosin hydrochloride is an antagonist of alpha$_{1A}$ adrenoceptors in the prostate.

Tamsulosin HCl is (-)-(*R*)-5-[2-[[2-(0-ethoxyphenoxy) ethyl]amino]propyl]-2-methoxybenzenesulfonamide, monohydrochloride. Tamsulosin HCl occurs as white crystals that melt with decomposition at approximately 230°C. It is sparingly soluble in water and in methanol, slightly soluble in glacial acetic acid and in ethanol, and practically insoluble in ether.

The empirical formula of tamsulosin HCl is $C_{20}H_{28}N_2O_5S \cdot HCl$. The molecular weight of tamsulosin HCl is 444.98. Its structural formula is:



Each FLOMAX capsule for oral administration contains tamsulosin HCl 0.4 mg, and the following inactive ingredients: methacrylic acid copolymer, microcrystalline cellulose, triacetin, polysorbate 80, sodium lauryl sulfate, calcium stearate, talc, FD&C blue No. 2, titanium dioxide, ferric oxide, gelatin, and trace amounts of shellac, industrial methylated spirit 74 OP, *n* -butyl alcohol, isopropyl alcohol, propylene glycol, dimethylpolysiloxane, and black iron oxide E172.

CLINICAL PHARMACOLOGY

The symptoms associated with benign prostatic hyperplasia (BPH) are related to bladder outlet obstruction, which is comprised of two underlying components: static and dynamic. The static component is related to an increase in prostate size caused, in part, by a proliferation of smooth muscle cells in the prostatic stroma. However, the severity of BPH symptoms and the degree of urethral obstruction do not correlate well with the size of the prostate. The dynamic component is a function of an increase in smooth muscle tone in the prostate and bladder neck leading to constriction of the bladder outlet. Smooth muscle tone is mediated by the sympathetic nervous stimulation of alpha$_1$ adrenoceptors, which are abundant in the prostate, prostatic capsule, prostatic urethra, and bladder neck. Blockade of these adrenoceptors can cause smooth muscles in the bladder neck and prostate to relax, resulting in an improvement in urine flow rate and a reduction in symptoms of BPH.

Tamsulosin, an alpha$_1$ adrenoceptor blocking agent, exhibits selectivity for alpha$_1$ receptors in the human prostate. At least three discrete alpha$_1$ -adrenoceptor subtypes have been identified: alpha$_{1A}$, alpha$_{1B}$ and alpha $_{1D}$; their distribution differs between human organs and tissue. Approximately 70% of the alpha$_1$-receptors in human prostate are of the alpha$_{1A}$ subtype.

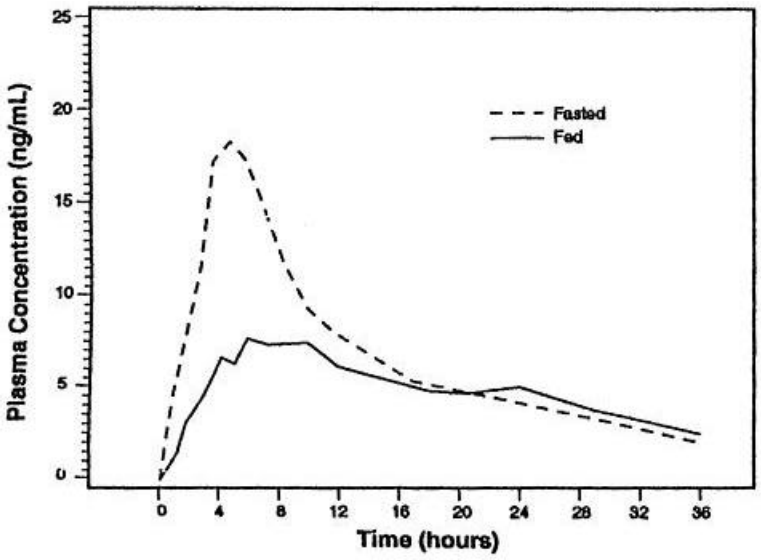
FLOMAX capsules are not intended for use as an antihypertensive drug.

Pharmacokinetics The pharmacokinetics of tamsulosin HCl have been evaluated in adult healthy volunteers and patients with BPH after single and/or multiple administration with doses ranging from 0.1 mg to 1 mg.

Absorption: Absorption of tamsulosin HCl from FLOMAX capsules 0.4 mg is essentially complete (>90%) following oral administration under fasting conditions. Tamsulosin HCl exhibits linear kinetics following single and multiple dosing, with achievement of steady-state concentrations by the fifth day of once-a-day dosing.

Effect of Food: The time to maximum concentration (T_{max}) is reached by four to five hours under fasting conditions and by six to seven hours when FLOMAX capsules are administered with food. Taking FLOMAX capsules under fasted conditions results in a 30% increase in bioavailability (AUC) and 40% to 70% increase in peak concentrations (C_{max}) compared to fed conditions (Figure 1).

Figure 1: Mean Plasma Tamsulosin HCl Concentrations Following Single-Dose Administration of FLOMAX capsules 0.4 mg Under Fasted and Fed Conditions (n=8).



The effects of food on the pharmacokinetics of tamsulosin HCl are consistent regardless of whether a FLOMAX capsule is taken with a light breakfast or a high-fat breakfast (Table 1).

TABLE 1 Mean (± S.D.) Pharmacokinetic Parameters Following FLOMAX capsules 0.4 mg Once Daily or 0.8 mg Once Daily with a Light Breakfast, High-Fat Breakfast or Fasted

Pharmacokinetic Parameter	0.4 mg q.d. to healthy volunteers; n=23 (age range 18-32 years)		0.8 mg q.d. to healthy volunteers; n=22 (age range 55-75 years)		
	Light Breakfast	Fasted	Light Breakfast	High-Fat Breakfast	Fasted
Cmin (ng/mL)	4.0 ± 2.6	3.8 ± 2.5	12.3 ± 6.7	13.5 ± 7.6	13.3 ± 13.3
Cmax (ng/mL)	10.1 ± 4.8	17.1 ± 17.1	29.8 ± 10.3	29.1 ± 11.0	41.6 ± 15.6
Cmax/Cmin Ratio	3.1 ± 1.0	5.3 ± 2.2	2.7 ± 0.7	2.5 ± 0.8	3.6 ± 1.1
Tmax (hours)	6.0	4.0	7.0	6.6	5.0
T1/2 (hours)	-	-	-	-	14.9 ± 3.9
AUC $_{[tgr]}$ (ng·hr/mL)	151 ± 81.5	199 ± 94.1	440 ± 195	449 ± 217	557 ± 257

Cmin = observed minimum concentration
Cmax = observed maximum tamsulosin HCl plasma concentration
Tmax = median time-to-maximum concentration
T1/2 = observed half-life
AUC $_t$ = Area under the tamsulosin HCl plasma time curve over the dosing interval

Distribution: The mean steady-state apparent volume of distribution of tamsulosin HCl after intravenous administration to ten healthy male adults was 16L, which is suggestive of distribution into extracellular fluids in the body. Additionally, whole body autoradiographic studies in mice and rats and tissue distribution in rats and dogs indicate that tamsulosin HCl is widely distributed to most tissues including kidney, prostate, liver, gall bladder, heart, aorta, and brown fat, and minimally distributed to the brain, spinal cord, and testes. Tamsulosin HCl is extensively bound to human plasma proteins (94% to 99%), primarily alpha-1 acid glycoprotein (AAG), with linear binding over a wide concentration range (20 to 600

ng/mL). The results of two-way *in vitro* studies indicate that the binding of tamsulosin HCl to human plasma proteins is not affected by amitriptyline, diclofenac, glyburide, simvastatin plus simvastatin-hydroxy acid metabolite, warfarin, diazepam, propranolol, trichlormethiazide, or chlormadinone. Likewise, tamsulosin HCl had no effect on the extent of binding of these drugs.

Metabolism: There is no enantiometric bioconversion from tamsulosin HCl [R(-) isomer] to the S(+) isomer in humans. Tamsulosin HCl is extensively metabolized by cytochrome P450 enzymes in the liver and less than 10% of the dose is excreted in urine unchanged. However, the pharmacokinetic profile of the metabolites in humans has not been established. Additionally, the cytochrome P450 enzymes that primarily catalyze the Phase I metabolism of tamsulosin HCl have not been conclusively identified. Therefore, possible interactions with other cytochrome P450 metabolized compounds cannot be discerned with current information. The metabolites of tamsulosin HCl undergo extensive conjugation to glucuronide or sulfate prior to renal excretion.

Incubations with human liver microsomes showed no evidence of clinically significant metabolic interactions between tamsulosin HCl and amitriptyline, albuterol (beta agonist), glyburide (glibenclamide) and finasteride (5alpha-reductase inhibitor for treatment of BPH). However, results of the *in vitro* testing of the tamsulosin HCl interaction with diclofenac and warfarin were equivocal.

Excretion: On administration of the radiolabeled dose of tamsulosin HCl to four healthy volunteers, 97% of the administered radioactivity was recovered, with urine (76%) representing the primary route of excretion compared to feces (21%) over 168 hours. Following intravenous or oral administration of an immediate-release formulation, the elimination half-life of tamsulosin HCl in plasma range from five to seven hours. Because of absorption rate-controlled pharmacokinetics with FLOMAX capsules, the apparent half-life of tamsulosin HCl is approximately 9 to 13 hours in healthy volunteers and 14 to 15 hours in the target population. Tamsulosin HCl undergoes restrictive clearance in humans, with a relatively low systemic clearance (2.88 L/h).

Special Populations: Geriatrics (Age): Cross-study comparison of FLOMAX capsules overall exposure (AUC) and half-life indicate that the pharmacokinetic disposition of tamsulosin HCl may be slightly prolonged in geriatric males compared to young, healthy male volunteers. Intrinsic clearance is independent of tamsulosin HCl binding to AAG, but diminishes with age, resulting in a 40% overall higher exposure (AUC) in subjects of age 55 to 75 years compared to subjects of age 20 to 32 years.

Renal Dysfunction: The pharmacokinetics of tamsulosin HCl have been compared in 6 subjects with mild - moderate ($30 \leq CL_{cr} < 70$ mL/min/1.73m^2) or moderate-severe ($10 \leq CL_{cr} < 30$ mL/min/1.73m^2) renal impairment and 6 normal subjects ($CL_{cr} < 90$ mL/min/1.73m^2). While a change in the overall plasma concentration of tamsulosin HCl was observed as the result of altered binding to AAG, the unbound (active) concentration of tamsulosin HCl, as well as the intrinsic clearance, remained relatively constant. Therefore, patients with renal impairment do not require an adjustment in FLOMAX capsules dosing. However, patients with endstage renal disease ($CL_{cr} < 10$ mL/min/1.73m^2) have not been studied.

Hepatic Dysfunction: The pharmacokinetics of tamsulosin HCl have been compared in 8 subjects with moderate hepatic dysfunction (Child-Pugh's classification: Grades A and B) and 8 normal subjects. While a change in the overall plasma concentration of tamsulosin HCl was observed as the result of altered binding to AAG, the unbound (active) concentration of tamsulosin HCl does not change significantly with only a modest (32%) change in intrinsic clearance of unbound tamsulosin HCl. Therefore, patients with moderate hepatic dysfunction do not require an adjustment in FLOMAX capsules dosage.

Drug-Drug Interactions: Nifedipine, Atenolol, Enalapril: In three studies in hypertensive subjects (age range 47-79 years) whose blood pressure was controlled with stable doses of Procardia XL®, atenolol, or enalapril for at least three months, FLOMAX capsules 0.4 mg for seven days followed by FLOMAX capsules 0.8 mg for another seven days (n=8 per study) resulted in no clinically significant effects on blood pressure and pulse rate compared to placebo (n=4 per study). Therefore, dosage adjustments are not necessary when FLOMAX capsules are administered concomitantly with Procardia XL®, atenolol, or enalapril.

Warfarin: A definitive drug-drug interaction study between tamsulosin HCl and warfarin was not conducted. Results from limited *in vitro* and *in vivo* studies are inconclusive. Therefore, caution should be exercised with concomitant administration of warfarin and FLOMAX capsules.

Digoxin and Theophylline: In two studies in healthy volunteers (n=10 per study; age range 19-39 years) receiving FLOMAX capsules 0.4 mg/day for two days, followed by FLOMAX capsules 0.8 mg/day for five to eight days, single intravenous doses of digoxin 0.5 mg or theophylline 5 mg/kg resulted in no change in the pharmacokinetics of digoxin or theophylline. Therefore, dosage adjustments are not necessary when a FLOMAX capsule is administered concomitantly with digoxin or theophylline.

Furosemide: The pharmacokinetic and pharmacodynamic interaction between FLOMAX capsules 0.8 mg/day (steady-state) and furosemide 20 mg intravenously (single dose) was evaluated in ten healthy volunteers (age range 21-40 years). FLOMAX capsules had no effect on the pharmacodynamics (excretion of electrolytes) of furosemide. While furosemide produced an 11% to 12% reduction in tamsulosin HCl Cmax and AUC, these changes are expected to be clinically insignificant and do not require adjustment of the FLOMAX capsules dosage.

Cimetidine: The effects of cimetidine at the highest recommended dose (400 mg every six hours for six days) on the pharmacokinetics of a single FLOMAX capsule 0.4 mg dose was investigated in ten healthy volunteers (age range 21-38 years). Treatment with cimetidine resulted in a significant decrease (26%) in the clearance of tamsulosin HCl which resulted in a moderate increase in tamsulosin HCl AUC (44%). Therefore, FLOMAX capsules should be used with caution in combination with cimetidine, particularly at doses higher than 0.4 mg.

Clinical Studies Four placebo-controlled clinical studies and one active-controlled clinical study enrolled a total of 2296 patients (1003 received FLOMAX capsules 0.4 mg once daily, 491 received FLOMAX capsules 0.8 mg once daily, and 802 were control patients) in the U.S. and Europe.

In the two U.S. placebo-controlled, double-blind, 13-week, multicenter studies [Study 1 (US92-03A) and Study 2 (US93-01)], 1486 men with the signs and symptoms of BPH were enrolled. In both studies, patients were randomized to either placebo, FLOMAX capsules 0.4 mg once daily, or FLOMAX capsules 0.8 mg once daily. Patients in FLOMAX capsules 0.8-mg once daily treatment groups received a dose of 0.4 mg once daily for one week before increasing to the 0.8-mg once daily dose. The primary efficacy assessments included: 1) total American Urological Association (AUA) Symptom Score questionnaire, which evaluated irritative (frequency, urgency, and nocturia), and obstructive (hesitancy, incomplete emptying, intermittency, and weak stream) symptoms, where a decrease in score is consistent with improvement in symptoms; and 2) peak urine flow rate, where an increased peak urine flow rate value over baseline is consistent with decreased urinary obstruction.

Mean changes from baseline to week 13 in total AUA Symptom Score were significantly greater for groups treated with FLOMAX capsules 0.4 mg and 0.8 mg once daily compared to placebo in both U.S. studies (Table 2, Figures 2A and 2B). The changes from baseline to week 13 in peak urine flow rate were also significantly greater for the FLOMAX capsules 0.4-mg and 0.8-mg once daily groups compared to placebo in Study 1, and for the FLOMAX capsules 0.8-mg once daily group in Study 2 (Table 2, Figures 3A and 3B). Overall there were no significant differences in improvement observed in total AUA Symptom Scores or peak urine flow rates between the 0.4-mg and the 0.8-mg dose groups with the exception that the 0.8-mg dose in Study 1 had a significantly greater improvement in total AUA Symptom Score compared to the 0.4-mg dose.

TABLE 2 MEAN (± S.D.) CHANGES FROM BASELINE TO WEEK 13 IN TOTAL AUA SYMPTOM SCORE ** AND PEAK URINE FLOW RATE (ML/SEC)

	Total AUA Symptom Score		Peak Urine Flow Rate	
	Mean Baseline Value	Mean Change	Mean Baseline Value	Mean Change
Study 1 H				
FLOMAX capsules 0.8 mg once daily	19.9±4.9 n=247	-9.6 * ±6.7 n=237	9.57±2.51 n=247	1.78 * ±3.35 n=247
FLOMAX capsules 0.4 mg once daily	19.8±5.0 n=254	-8.3 * ±6.5 n=246	9.46±2.49 n=254	1.75 * ±3.57 n=254
Placebo	19.6±4.9 n=254	-5.5±6.6 n=246	9.75±2.54 n=254	0.52±3.39 n=253
Study 2 I				

FLOMAX capsules 0.8 mg once daily	18.2±5.6 n=244	-5.8 * ±6.4 n=238	9.96±3.16 n=244	1.79 * ±3.36 n=237
FLOMAX capsules 0.4 mg once daily	17.9±5.8 n=248	-5.1 * ±6.4 n=244	9.94±3.14 n=248	1.52±3.64 n=244
Placebo	19.2±6.0 n=239	-3.6±5.7 n=235	9.95±3.12 n=239	0.93±3.28 n=235

* Statistically significant difference from placebo (p-value ≤0.050; Bonferroni-Holm multiple test procedure);

** Total AUA Symptom Scores ranged from 0 to 35

H Peak urine flow rate measured 4 to 8 hours post dose at week 13

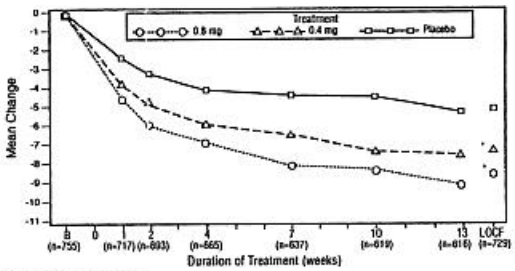
I Peak urine flow rate measured 24 to 27 hours post dose at week 13

Week 13: For patients not completing the 13 week study the last observation was carried forward.

Mean total AUA Symptom Scores for both FLOMAX capsules 0.4-mg and 0.8-mg once daily groups showed a rapid decrease starting at one week after dosing and remained decreased through 13 weeks in both studies (Figures 2A and 2B).

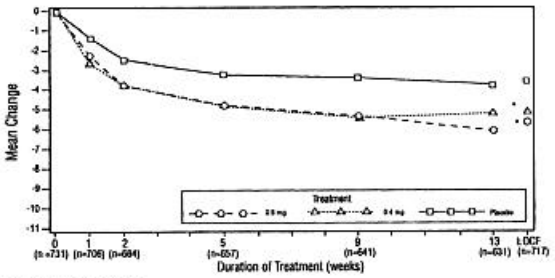
In Study 1, 400 patients (53% of the originally randomized group) elected to continue in their originally assigned treatment groups in a double-blind, placebo controlled, 40 week extension trial (138 patients on 0.4 mg, 135 patients on0.8 mg and 127 patients on placebo). Three hundred and twenty-three patients (43% of the originally randomized group) completed one year. Of these, 81% (97 patients) on 0.4 mg, 74% (75 patients) on 0.8 mg and 56% (57 patients) on placebo had a response ≥25% above baseline in total AUA Symptom Score at one year.

FIGURE 2A:
Mean Change from Baseline in Total AUA Symptom Score (0-35) Study 1



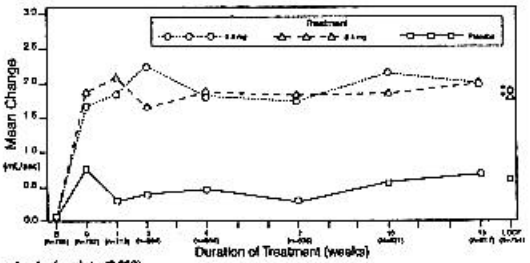
* indicates significant difference from placebo (p-value ≤0.050).
B=Baseline determined approximately one week prior to the initial dose of double-blind medication at Week 0. Subsequent values are observed cases.
LOCF= Last observation carried forward for patients not completing the 13-week study.
Note: Patients in the 0.8 mg treatment group received 0.4 mg for the first week.
Note: Total AUA Symptom Scores range from 0 to 35.

FIGURE 2B:
Mean Change from Baseline in Total AUA Symptom Score (0-35) Study 2



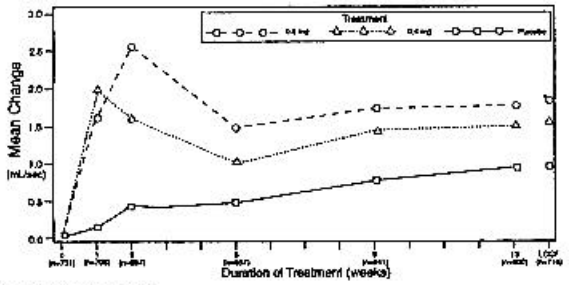
* indicates significant difference from placebo (p-value ≤0.050).
Baseline measurement was taken Week 0. Subsequent values are observed cases.
LOCF= Last observation carried forward for patients not completing the 13-week study.
Note: Patients in the 0.8 mg treatment group received 0.4 mg for the first week.
Note: Total AUA Symptom Scores range from 0 to 35.

FIGURE 3A:
Mean Increase in Peak Urine Flow Rate (mL/Sec) Study 1



* indicates significant difference from placebo (p-value ≤0.050).
B=Baseline determined approximately one week prior to the initial dose of double-blind medication at Week 0. Subsequent values are observed cases.
LOCF= Last observation carried forward for patients not completing the 13-week study.
Note: The uroflowmetry assessments at week 0 were recorded 4-8 hours after patients received the first dose of double-blind medication.
Measurements at each visit were scheduled 4-8 hours after dosing (approximately peak plasma tamsulosin concentration).
Note: Patients in the 0.8 mg treatment groups received 0.4 for the first week.

FIGURE 3B:
Mean Increase in Peak Urine Flow Rate (mL/Sec) Study 2



* Indicates significant difference from placebo (p-value ≤0.050).
Baseline measurement was taken Week 0. Subsequent values are observed cases.
LOCF=Last observation carried forward for patients not completing the 13-week study.
Note: Patients in the 0.8 mg treatment group received 0.4 mg for the first week.
Note: Week 1 and Week 2 measurements were scheduled 4-8 hours after dosing (approximate peak plasma tamsulosin concentration).
All other visits were scheduled 24-27 hours after dosing (approximate trough tamsulosin concentration).

INDICATIONS AND USAGE

FLOMAX ® (tamsulosin HCl) capsules are indicated for the treatment of the signs and symptoms of benign prostatic hyperplasia (BPH). FLOMAX capsules are not indicated for the treatment of hypertension.

CONTRAINDICATIONS

FLOMAX capsules are contraindicated in patients known to be hypersensitive to tamsulosin HCl or any component of FLOMAX capsules.

WARNINGS

The signs and symptoms of orthostasis (postural hypotension, dizziness and vertigo) were detected more frequently in FLOMAX capsule treated patients than in placebo recipients. As with other alpha-adrenergic blocking agents there is a potential risk of syncope (see ADVERSE REACTIONS).

Patients beginning treatment with FLOMAX capsules should be cautioned to avoid situations where injury could result should syncope occur.

Rarely (probably less than one in fifty thousand patients), tamsulosin, like other alpha $_1$ antagonists, has been associated with priapism (persistent painful penile erection unrelated to sexual activity). Because this condition can lead to permanent impotence if not properly treated, patients must be advised about the seriousness of the condition (see Precautions : Information for Patients).

PRECAUTIONS

General

1) Carcinoma of the prostate: Carcinoma of the prostate and BPH cause many of the same symptoms. These two diseases frequently co-exist. Patients should be evaluated prior to the start of FLOMAX capsules therapy to rule out the presence of carcinoma of the prostate.

2) Drug-Drug Interactions: The pharmacokinetic and pharmacodynamic interactions between FLOMAX capsules and other alpha-adrenergic blocking agents have not been determined. However, interactions may be expected and FLOMAX capsules should NOT be used in combination with other alpha-adrenergic blocking agents.

The pharmacokinetic interaction between cimetidine and FLOMAX capsules was investigated. The results indicate significant changes in tamsulosin HCl clearance (26% decrease) and AUC (44% increase). Therefore, FLOMAX capsules should be used with caution in combination with cimetidine, particularly at doses higher than 0.4 mg.

Results from limited *in vitro* and *in vivo* drug-drug interaction studies between tamsulosin HCl and warfarin are inconclusive. Therefore, caution should be exercised with concomitant administration of warfarin and FLOMAX capsules.

(See also drug-drug interaction studies in CLINICAL PHARMACOLOGY , Pharmacokinetics subsection .)

Information for Patients (see Patient Package Insert)

Patients should be told about the possible occurrence of symptoms related to postural hypotension such as dizziness when taking FLOMAX capsules, and they should be cautioned about driving, operating machinery or performing hazardous tasks.

Patients should be advised not to crush, chew or open the FLOMAX capsules.

Patients should be advised about the possibility of priapism as a result of treatment with FLOMAX Capsules and other similar medications. Patients should be informed that this reaction is extremely rare, but if not brought to immediate medical attention, can lead to permanent erectile dysfunction (impotence).

Laboratory Tests

No laboratory test interactions with FLOMAX capsules are known. Treatment with FLOMAX capsules for up to 12 months had no significant effect on prostate-specific antigen (PSA).

Pregnancy Teratogenic Effects, Pregnancy Category B. Administration of tamsulosin HCl to pregnant female rats at dose levels up to 300 mg/kg/day (approximately 50 times the human therapeutic AUC exposure) revealed no evidence of harm to the fetus. Administration of tamsulosin HCl to pregnant rabbits at dose levels up to 50 mg/kg/day produced no evidence of fetal harm. FLOMAX capsules are not indicated for use in women.

Nursing Mothers FLOMAX capsules are not indicated for use in women.

Pediatric Use FLOMAX capsules are not indicated for use in pediatric populations.

Carcinogenesis, Mutagenesis, and Impairment of Fertility Rats administered doses up to 43 mg/kg/day in males and 52 mg/kg/day in females had no increases in tumor incidence with the exception of a modest increase in the frequency of mammary gland fibroadenomas in female rats receiving doses ≥5.4 mg/kg ($P < 0.015$). The highest doses of tamsulosin HCl evaluated in the rat carcinogenicity study produced systemic exposures (AUC) in rats 3 times the exposures in men receiving the maximum therapeutic dose of0.8 mg/day.

Mice were administered doses up to 127 mg/kg/day in males and 158 mg/kg/day in females. There were no significant tumor findings in male mice. Female mice treated for 2 years with the two highest doses of 45 and 158 mg/kg/day had statistically significant increases in the incidence of mammary gland fibroadenomas ($P< 0.0001$) and adenocarcinomas ($P< 0.0075$). The highest dose levels of tamsulosin HCl evaluated in the mice carcinogenicity study produced systemic exposures (AUC) in mice 8 times the exposures in men receiving the maximum therapeutic dose of 0.8 mg/day.

The increased incidences of mammary gland neoplasms in female rats and mice were considered secondary to tamsulosin HCl-induced hyperprolactinemia. It is not known if FLOMAX capsules elevate prolactin in humans. The relevance for human risk of the findings of prolactin-mediated endocrine tumors in rodents is not known.

Tamsulosin HCl produced no evidence of mutagenic potential *in vitro* in the Ames reverse mutation test, mouse lymphoma thymidine kinase assay, unscheduled DNA repair synthesis assay, and chromosomal aberration assays in Chinese hamster ovary cells or human lymphocytes. There were no mutagenic effects in the *in vivo* sister chromatid exchange and mouse micronucleus assay.

Studies in rats revealed significantly reduced fertility in males dosed with single or multiple daily doses of 300 mg/kg/day of tamsulosin HCl (AUC exposure in rats about 50 times the human exposure with the maximum therapeutic dose). The mechanism of decreased fertility in male rats is considered to be an effect of the compound on the vaginal plug formation possibly due to changes of semen content or impairment of ejaculation. The effects on fertility were reversible showing improvement by 3 days after a single dose and 4 weeks after multiple dosing. Effects on fertility in males were completely reversed within nine weeks of discontinuation of multiple dosing. Multiple doses of 10 and 100 mg/kg/day tamsulosin HCl (1/5 and 16 times the anticipated human AUC exposure) did not significantly alter fertility in male rats. Effects of tamsulosin HCl on sperm counts or sperm function have not been evaluated. Studies in females rats revealed significant reductions in fertility after single or multiple dosing with 300 mg/kg/day of the R-isomer or racemic mixture of tamsulosin HCl, respectively. In female rats, the

reductions in fertility after single doses were considered to be associated with impairments in fertilization. Multiple dosing with 10 or 100 mg/kg/day of the racemic mixture did not significantly alter fertility in female rats.

ADVERSE REACTIONS

The incidence of treatment-emergent adverse events has been ascertained from six short-term U.S. and European placebo-controlled clinical trials in which daily doses of 0.1 to 0.8 mg FLOMAX capsules were used. These studies evaluated safety in 1783 patients treated with FLOMAX capsules and 798 patients administered placebo. Table 3 summarizes the treatment-emergent adverse events that occurred in ≥2% of patients receiving either FLOMAX capsules 0.4 mg, or 0.8 mg and at an incidence numerically higher than that in the placebo group during two 13-week U.S. trials (US92-03A and US93-01) conducted in 1487 men.

TABLE 3. TREATMENT EMERGENT[1] ADVERSE EVENTS OCCURRING IN ³ 2% OF FLOMAX CAPSULES OR PLACEBO PATIENTS IN TWO U.S. SHORT-TERM PLACEBO-CONTROLLED CLINICAL STUDIES

BODY SYSTEM/ ADVERSE EVENT	FLOMAX CAPSULES GROUPS		PLACEBO
	0.4 mg n=502	0.8 mg n=492	n=493
BODY AS WHOLE			
Headache	97(19.3%)	104(21.1%)	99(20.1%)
Infection	45(9.0%)	53(10.8%)	37(7.5%)
Asthenia	39(7.8%)	42(8.5%)	27(5.5%)
Back Pain	35(7.0%)	41(8.3%)	27(5.5%)
Chest Pain	20(4.0%)	20(4.1%)	18(3.7%)
NERVOUS SYSTEM			
Dizziness	75(14.9%)	84(17.1%)	50(10.1%)
Somnolence	15(3.0%)	21(4.3%)	8(1.6%)
Insomnia	12(2.4%)	7(1.4%)	3(0.6%)
Libido Decreased	5(1.0%)	10(2.0%)	6(1.2%)
RESPIRATORY SYSTEM			
Rhinitis	66(13.1%)	88(17.9%)	41(8.3%)
Pharyngitis	29(5.8%)	25(5.1%)	23(4.7%)
Cough Increased	17(3.4%)	22(4.5%)	12(2.4%)
Sinusitis	11(2.2%)	18(3.7%)	8(1.6%)
DIGESTIVE SYSTEM			
Diarrhea	31(6.2%)	21(4.3%)	22(4.5%)
Nausea	13(2.6%)	19(3.9%)	16(3.2%)
Tooth Disorder	6(1.2%)	10(2.0%)	7(1.4%)
UROGENITAL SYSTEM			
Abnormal Ejaculation	42(8.4%)	89(18.1%)	1(0.2%)
SPECIAL SENSES			
Amblyopia	1(0.2%)	10(2.0%)	2(0.4%)

[1] A treatment-emergent adverse event was defined as any event satisfying one of the following criteria:

- The adverse event occurred for the first time after initial dosing with double-blind study medication.
- The adverse event was present prior to or at the time of initial dosing with double-blind study medication and subsequently increased in severity during double-blind treatment;
  or
- The adverse event was present prior to or at the time of initial dosing with double-blind study medication, disappeared completely, and then reappeared during double-blind treatment.

Signs and Symptoms of Orthostasis In the two U.S. studies, symptomatic postural hypotension was reported by 0.2% of patients (1 of 502) in the 0.4-mg group, 0.4% of patients (2 of 492) in the 0.8-mg group, and by no patients in the placebo group. Syncope was reported by 0.2% of patients (1 of 502) in the 0.4-mg group, 0.4% of patients (2 of 492) in the 0.8-mg group and 0.6% of patients (3 of 493) in the placebo group. Dizziness was reported by 15% of patients (75 of 502) in the 0.4-mg group, 17% of patients (84 of 492) in the 0.8-mg group, and 10% of patients (50 of 493) in the placebo group. Vertigo

was reported by 0.6% of patients (3 of 502) in the 0.4-mg group, 1% of patients (5 of 492) in the 0.8 mg group and by 0.6% of patients (3 of 493) in the placebo group.

Multiple testing for orthostatic hypotension was conducted in a number of studies. Such a test was considered positive if it met one or more of the following criteria: (1) a decrease in systolic blood pressure of ≥20 mmHg upon standing from the supine position during the orthostatic tests; (2) a decrease in diastolic blood pressure ≥10mmHg upon standing, with the standing diastolic blood pressure <65 mmHg during the orthostatic test; (3) an increase in pulse rate of ≥20 bpm upon standing with a standing pulse rate ≥100 bpm during the orthostatic test; and (4) the presence of clinical symptoms (faintness, lightheadedness/lightheaded, dizziness, spinning sensation, vertigo, or postural hypotension) upon standing during the orthostatic test.

Following the first dose of double-blind medication in Study 1, a positive orthostatic test result at 4 hours post-dose was observed in 7% of patients (37 of 498) who received FLOMAX capsules 0.4 mg once daily and in 3% of the patients (8 of 253) who received placebo. At 8 hours post-dose, a positive orthostatic test result was observed for 6% of the patients (31 of 498) who received FLOMAX capsules 0.4 mg once daily and 4% (9 of 250) who received placebo (Note: patients in the 0.8-mg group received 0.4 mg once daily for the first week of Study 1).

In Studies 1 and 2, at least one positive orthostatic test result was observed during the course of these studies for 81 of the 502 patients (16%) in the FLOMAX capsules 0.4-mg once daily group, 92 of the 491 patients (19%) in the FLOMAX capsules 0.8-mg once daily group and 54 of the 493 patients (11%) in the placebo group.

Because orthostasis was detected more frequently in FLOMAX capsule-treated patients than in placebo recipients, there is a potential risk of syncope (see WARNINGS).

Abnormal Ejaculation Abnormal ejaculation includes ejaculation failure, ejaculation disorder, retrograde ejaculation and ejaculation decrease. As shown in Table 3, abnormal ejaculation was associated with FLOMAX capsules administration and was dose-related in the U.S. studies. Withdrawal from these clinical studies of FLOMAX capsules because of abnormal ejaculation was also dose-dependent with 8 of 492 patients (1.6%) in the 0.8-mg group, and no patients in the 0.4-mg or placebo groups discontinuing treatment due to abnormal ejaculation.

Post-Marketing Experience Allergic-type reactions such as skin rash, pruritus, angioedema of tongue, lips and face and urticaria have been reported with positive rechallenge in some cases. Priapism has been reported rarely. Infrequent reports of palpitations, constipation and vomiting have been received during the post-marketing period.

OVERDOSAGE

Should overdosage of FLOMAX capsules lead to hypotension (See WARNINGS and ADVERSE REACTIONS), support of the cardiovascular system is of first importance. Restoration of blood pressure and normalization of heart rate may be accomplished by keeping the patient in the supine position. If this measure is inadequate, then administration of intravenous fluids should be considered. If necessary, vasopressors should then be used and renal function should be monitored and supported as needed. Laboratory data indicate that tamsulosin HCl is 94% to 99% protein bound; therefore, dialysis is unlikely to be of benefit.

One patient reported an overdose of thirty 0.4-mg FLOMAX capsules. Following the ingestion of the capsules, the patient reported a severe headache.

DOSAGE AND ADMINISTRATION

FLOMAX capsules 0.4 mg once daily is recommended as the dose for the treatment of the signs and symptoms of BPH. It should be administered approximately one-half hour following the same meal each day.

For those patients who fail to respond to the 0.4-mg dose after two to four weeks of dosing, the dose of FLOMAX capsules can be increased to 0.8 mg once daily. If FLOMAX capsules administration is

discontinued or interrupted for several days at either the 0.4-mg or 0.8-mg dose, therapy should be started again with the 0.4-mg once daily dose.

HOW SUPPLIED

FLOMAX capsules 0.4 mg are supplied in high density polyethylene bottles containing 100 or 1000 hard gelatin capsules with olive green opaque cap and orange opaque body. The capsules are imprinted on one side with "Flomax 0.4 mg" and on the other side with "BI 58."

NDC 0597-0058-01

FLOMAX Capsules

0.4 mg, 100 capsules

NDC 0597-0058-10

FLOMAX Capsules

0.4 mg, 1000 capsules

Rx only.

Store at controlled room temperature 20°-25° C (68°-77° F).

Keep FLOMAX capsules and all medicines out of reach of children

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FLOMAX®

(tamsulosin HCl) Capsules

PATIENT INFORMATION ABOUT

FLOMAX CAPSULES

FLOMAX capsules are for use by men only. **Flomax capsules are not indicated for use in women.**

Please read this leaflet before you start taking FLOMAX capsules. Also, read it each time you renew your prescription, just in case new information has been added. Remember, this leaflet does not take the place of careful discussions with your doctor. You and your doctor should discuss FLOMAX capsules when you start taking your medication and at regular checkups.

Why your doctor has prescribed FLOMAX capsules?

Your doctor has prescribed FLOMAX capsules because you have a medical condition called benign prostatic hyperplasia or BPH This occurs only in men.

What is BPH?

Benign prostatic hyperplasia is an enlargement of the prostate gland. After age 50, most men develop enlarged prostates. The prostate is located below the bladder. As the prostate enlarges, it may slowly restrict the flow of urine. This can lead to symptoms such as:

• a weak or interrupted urinary stream

• a feeling that you cannot empty your bladder completely
• a feeling of delay or hesitation when you start to urinate
• a need to urinate often, especially at night
• a feeling that you must urinate right away

Since cancer of the prostate may cause similar symptoms, you should be evaluated by your doctor to rule out prostate cancer. Your doctor will likely examine your prostate gland manually to detect abnormalities and may measure prostate specific antigen (PSA) in your blood to help in evaluating for the presence of prostate cancer. FLOMAX capsules do not affect PSA levels.

Treatment Options for BPH

There are three main treatment options for BPH:

- Program of monitoring or "Watchful Waiting". Some men have an enlarged prostate gland, but no symptoms, or symptoms that are not bothersome. If this applies, you and your doctor may decide on a program of monitoring, including regular checkups, instead of medication or surgery.
- There are different kinds of medication used to treat BPH. Your doctor has prescribed FLOMAX capsules for you. See "What a FLOMAX capsule does to treat BPH" below.
- Surgery. Some patients may need surgery. Your doctor can describe several different surgical procedures to treat BPH. Which procedure is best depends on your symptoms and medical condition.

What a FLOMAX capsule does to treat BPH

FLOMAX capsules act by relaxing muscles in the prostate and bladder neck at the site of the obstruction, resulting in improved urine flow and reduced BPH symptoms.

What you need to know while taking FLOMAX@ (tamsulosin HCl) capsules

- **You must see your doctor regularly.**

  While taking FLOMAX capules, you must have regular checkups. Follow your doctor's advice about when to have these checkups.

- **It is important for you to recognize that FLOMAX capsules can cause a sudden drop in blood pressure especially following the first dose or when changing doses of FLOMAX capsules.** Such a drop in blood pressure, although rare in occurrence, may be associated with fainting, dizziness, or lightheadedness. Therefore, get up slowly from a chair or bed at any time until you learn how you react to FLOMAX capsules. You should not drive or do any hazardous tasks until you are used to the side effects of FLOMAX capsules. If you begin to feel dizzy, sit down until you feel better. Although these symptoms are unlikely, you should avoid driving or hazardous tasks for 12 hours after the initial dose or after your doctor recommends an increase in dose. If you interrupt your treatment for several days or more, resume treatment at one capsule a day, after consulting with your physician. Other side effects may include sleeplessness, runny nose, or ejaculatory problems. In some cases, side effects may decrease or disappear when you continue to take FLOMAX capsules.

- Extremely rarely, FLOMAX Capsules and similar medications have caused prolonged, painful erection of the penis, which is unrelieved by sexual intercourse or masturbation. This condition, if untreated, can lead to permanent inability to have an erection. If you have a prolonged erection, call your doctor or go an Emergency Room as soon as possible.

You should discuss side effects with your doctor before taking FLOMAX capsules and anytime you think you are having a side effect.

How to take FLOMAX capsules

Follow your doctor's advice about how to take FLOMAX capsules. You should take it approximately 30 minutes following the same meal every day.

Do not share FLOMAX capsules with anyone else; it was prescribed only for you.

Do not crush, chew, or open capsules of FLOMAX capsules.

Keep FLOMAX capsules and all medicines out of reach of children.

FOR MORE INFORMATION ABOUT FLOMAX CAPSULES AND BPH, TALK WITH YOUR DOCTOR. IN ADDITION, TALK TO YOUR PHARMACIST OR OTHER HEALTHCARE PROVIDER.

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